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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| RAO, MANJUNATH N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/917,378 | DING ET AL. | |
| | Examiner | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *10,11,26-34,43,44 and 63-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10 and 11* is/are allowed.

6)☒ Claim(s) *26-34,43,44,63-68 and 73* is/are rejected.

7)☒ Claim(s) *69-72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 10-11, 26-34, 43-44, and 63-73 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 5-15-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous objections in view of the claim amendments.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 64 and claims 65-73 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 64 recites the phrase "comprising a catalytic domain glycoside hydrolase family 5 (GH5)". The metes and bounds of the above phrase is not clear to the Examiner. The phrase as written does not make it clear as to what specific catalytic activity is encompassed by the above phrase. The term glycosidase is a very broad term and includes the hydrolysis of more than one type of glycosidic linkage, i.e., alpha 1, 4, or β 1,3-, or β 1,4-, etc. Therefore the scope of the above phrase is not clear to the Examiner.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-34, 43-44 and 63-68, 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mannanase with ß 1,4-mannosidase activity having the amino acid sequence SEQ ID NO:1 or comprising a sequence of SEQ ID NO:3:4:5 in that order and a fusion protein comprising the above amino acid sequences, does not reasonably provide enablement for any such enzyme or fusion proteins comprising an amino acid sequence that has at least 70% or 90% sequence identity to amino acid sequence SEQ ID NO:1 or comprising a sequence of SEQ ID NO:3:4:5 in that order, does not reasonably provide enablement for such a protein comprising any catalytic domain of any glycoside hydrolase of GH5 family. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 26-34, 43-44 and 63-68, 73 are so broad as to encompass any mannanase comprising an amino acid sequence having 70% or 90% identity to SEQ ID NO:1 or a

polypeptide comprising a sequence of SEQ ID NO:3:4:5 in that order or a protein comprising any catalytic domain of any glycoside hydrolase of GH5 family. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mannanases/glycosyl hydrolases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single mannanase comprising SEQ ID NO:1 or comprising a sequence of SEQ ID NO:3:4:5 in that order. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of SEQ ID NO:1 or polypeptide comprising a sequence of SEQ ID NO:3:4:5 in that order as a mannanase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, in order to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mannanase with 70% or 90% identity to the enzymes comprising SEQ ID NO:1 or comprising a sequence of SEQ ID NO:3:4:5 in that order because the specification does not establish: (A) regions of the protein structure which may be modified without affecting mannanase activity; (B) the general tolerance of mannanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in any mannanase polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including mannanases with an enormous number of amino acid modifications to SEQ ID NO:1 or polypeptide comprising a sequence of SEQ ID NO:3:4:5 in that order. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance,

determination of mannanases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection arguing that the requirements for enablement has been met. Applicant argues that he has provided compared the consensus sequences and provided the conserved sequences and great number of GH5, CBDII and CBDIII family domains are well known in the art. Applicant also argues that guidance for making deletions or substitutions have been discussed and suitable techniques provided in the specification. Applicant also argues that applying the "standard of reasonableness" to the situation in this art means it is not undue nor is it unexpected to encounter some failure and that some experimentation is not undue. Examiner respectfully disagrees with all the above arguments. The guidance provided in the specification are all general guidance and it is well within the skill of those practicing the art not to change or modify the conserved sequences or the consensus sequences. Furthermore applicant's argument that the "standard of reasonableness" to the situation in this art means it is not undue nor is it unexpected to encounter some failure and that some experimentation is not undue would have been appropriate if the variants claimed involved modification of one or two amino acids only. However, such is the not the case in this application. Applicants are claiming variants involving a large number of amino acid changes which requires specific guidance regarding specific amino acid residues that can be modified.

While, Examiner agrees that methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan,

producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance regarding specific amino acids residues that can be modified without affecting the specific function of the polypeptide. Furthermore, in case of substitution of amino acids residues, applicant needs to provide guidance regarding the amino acids suitable for substitution as well as guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting mannanase activity; (B) the general tolerance of mannanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claims 64- 68 and 73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 64-68, 73 are directed to composition comprising polypeptides having any glycosidase catalytic domain and two carbohydrate binding domains. Claims 64-68, 73 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residues in said polypeptides, that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1 and 3, 4, 5, has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species (SEQ ID NO:1, comprising SEQ ID NO:3,4,5) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

***Conclusion***

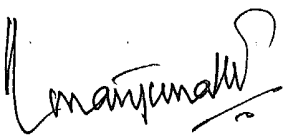
Claims 10 and 11 are allowable. Claims 69-72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 7.30 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0939. The fax phone numbers for the organization

where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.



Manjunath N. Rao
July 19, 2004